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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 45

mailed out date 8/19/99

Application Number: 08/225,478
Filing Date: April 8, 1994
Appellant(s): Donald B. Kohn, R. Michael Blaese, Craig A. Mullen and Robert C. Moen

Raymond J. Lillie
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed July 6, 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-3, 5, 21 and 22 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Kohn, D.B. et al. "Engraftment of gene-modified umbilical cord blood cells in neonates with adenosine deaminase deficiency." Nature Medicine, vol. 1, no. 10 (October 1995), pp. 1017-1023.

Orkin, S.H. et al. "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy." (December 7, 1995).

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-3, 5, 21 and 22 are rejected under 35 U.S.C. § 112, first paragraph. This rejection is set forth in prior Office action, Paper No. 33 (pp. 2-4).

(11) Response to Argument

Appellants argue, "The burden is upon the Examiner to show that one cannot genetically engineer autologous CD34+ cells with a nucleic acid sequence encoding a therapeutic agent, and/or cannot administer such genetically engineered cells to the human for expression of the therapeutic agent in the human." This statement frames the issue incorrectly. First, this Examiner (and previous examiners), have never taken the position that the methods cannot succeed. Inoperability would be the basis for a rejection under 35 U.S.C. § 101. Rather, the Examiner's burden is to present evidence that it would require undue experimentation to apply the claimed method for expression of therapeutic agents other than adenosine deaminase (ADA). Furthermore, the issue is not whether a nucleic acid sequence could be inserted into cells and the cells administered, but whether a therapeutic benefit would

result from such treatment. As pointed out previously (paper 36, p. 3), while the claims have been amended to remove the recitation of obtaining a therapeutic effect, they are still construed as a method of treatment because the specification does not disclose any other purpose for carrying out the claimed method. Therefore the issue at hand is whether it would require undue experimentation to develop the disclosed method for treatment of diseases other than ADA deficiency.

Appellants argue that they need not demonstrate that CD34+ cells can be engineered with every possible nucleic acid sequence. This is not the point. There is no doubt that any piece of DNA can be put into CD34+ cells. However, the fate of the transfected cells once they are re-introduced into the body is unpredictable. If the therapeutic agent is recognized by the body as "foreign," for example, the transfected cells may be eliminated by the immune system. If expression of the inserted DNA rapidly declines (a common problem), a therapeutic benefit may not be obtained. Also, for treatment of some diseases, mere expression of a protein is insufficient - correct regulation of expression is required. For example, unregulated expression of insulin is more likely to kill a patient (from hypoglycemia) than effect a cure. Another question is whether expression of a protein in CD34+ cells will deliver the protein to the tissue or cell type where it is needed. As Orkin et al. state, "Although 'gene addition' is the simplest strategy for somatic gene therapy, several practical difficulties need to be addressed...[including] achieving the level of expression required for correction, and regulating expression of the added gene once it is transferred into appropriate

target cells" (p. 5, paragraph 5). Appellants themselves have stated in a post-filing reference, "The successful application of gene therapy to other haematologic disorders where the transduced progenitors do not have a selective advantage...will require more efficient gene transfer. These advances will require better understanding of the biology of haematopoietic stem cells and the cytokines that regulate their proliferation" (Kohn et al., p. 1021, col. 2).

Appellants argue that the Orkin et al. report indicates that the skilled artisan would expect that the claimed method would be successful for expressing a variety of therapeutic agents (i.e. treating a variety of diseases). This argument is not persuasive. An objective reading of Orkin et al. indicates that well after the filing date of the instant application, those skilled in the art expected that considerable further experimentation, including much basic biological research, would be required before gene therapy methods would be successful. "Typically, many years are required before new therapies are proved successful" (Orkin et al., p. 4, paragraph 4). With regard to the 597 individuals having undergone gene transfer, the majority were not enrolled in trials for treatment of an inherited disease (p. 12, last paragraph). Furthermore, these trials are little more than experiments, not successful treatments. "Although widely referred to as 'clinical trials,' gene transfer protocols to date are in truth smallscale clinical experiments. Such exploratory studies are meant to test the feasibility and safety of administering particular vectors and...have not been designed to measure efficacy" (p. 13, first paragraph, emphasis added).

In conclusion, the art of record indicates that, even after the filing date of the instant application, it would have required much more than routine experimentation for one skilled in the art to practice the claimed gene therapy methods for treatment of any disease other than ADA deficiency. This is particularly true given the nature of the invention, the state of the art, the absence of any specific guidance in the specification regarding which coding sequences and regulatory sequences should be used to treat which diseases, and the unpredictable nature of the art. Thus a *prima facie* case for non-enablement of the full scope of the claims has been established.

Appellants have chosen to argue that no *prima facie* case exists. While criticizing the references cited by the Office, Appellants have not presented any evidence to counter these references. No reference indicating that gene therapy was a routine matter as of 1994, to contradict Orkin et al., has been provided. No evidence showing that Appellants or others have practiced the claimed method to treat other diseases has been presented. Orkin et al. reported that over 100 protocols had been approved. Four years later, where are the results

proving the efficacy of gene therapy? Thus the *prima facie* case for non-enablement has not been rebutted.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Bruce Campell

BRC
August 19, 1999

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